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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/630,375	07/29/2003	Michel Schneider	BR029-US-02	8951
7590 Bracco Research USA 305 College Road East Princeton, NJ 08540				
EXAMINER				
EBRAHIM, NABILA G				
ART UNIT		PAPER NUMBER		
1618				
MAIL DATE		DELIVERY MODE		
05/20/2009		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/630,375

**Applicant(s)**

SCHNEIDER ET AL.

**Examiner**

Nabila G. Ebrahim

**Art Unit**

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**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 05 January 2009.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 1-52 is/are pending in the application.
- 4a) Of the above claim(s) 1-15 and 33-46 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 16-32 and 47-52 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S508)
- Paper No(s)/Mail Date \_\_\_\_\_

- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date \_\_\_\_\_
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_

### **DETAILED ACTION**

Receipt of Applicant's arguments dated 02/26/2008 is acknowledged.

#### ***Status of Claims***

Claims 1-52 are pending in the application.

Claims 16-32 and 47-52 are under current examination.

Claims 1-15 and 33-46 were withdrawn from consideration due to election/restriction requirement.

***Status of Office Action:*** Non-Final.

#### ***Claim Rejections - 35 USC § 112***

1. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

2. Claims 49 and 52 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The claims recite "hydrophilic polymers like polyox-ypropylene glycol and polyoxyethylene glycol". It is unclear if the phrase, "like polyoxypolyethylene glycol and polyethylene glycol," is intended merely to provide examples of suitable hydrophilic polymers or whether it limits the hydrophilic polymers to these two possibilities.

#### ***Claim Rejections - 35 USC § 102***

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

1. Claim 16, 17, 21-24, 28-32 and 47-52 remain rejected under 35 U.S.C. 102(b) as being anticipated by Schneider et al. EP 0554213, published April 1993 (Schneider).

Schneider teaches microbubbles are advantageously formed from an aqueous liquid and a dry powder (microvesicle precursors) containing lamellarized freeze-dried phospholipids and stabilizers; the microbubbles are developed by agitation of this powder in admixture with the aqueous liquid carrier (page 4, lines 7+). The phospholipid is Dipalmitoylphosphatidylglycerol (example 8). Schneider explains that the vesicle suspensions, or preferably precursors thereof (precursors here may mean the materials the microvesicle envelopes are made of, or the materials which, upon agitation with an aqueous carrier liquid, will generate or develop the formation of microbubbles in this liquid), can be exposed to reduced pressure to evacuate the gas to be removed and then the ambient pressure is restored with the desired gas for substitution and that this step can be repeated once or more times to ensure complete replacement of the original gas by the new one (page 4, lines 29+). Further, Schneider teaches that it is advantageous to store this dry powder under an atmosphere of a gas selected according to the invention (page 4, lines 39+). In addition, the reference discloses that it has been surprisingly found that for gases where the pressure difference  $DP = P_{25} - P_{75}$  exceeds a value of about 25 - 30 Torr, the killing effect of the blood pressure on the gas-filled microvesicles is minimized (page 6, lines 20+). The gaseous species which particularly suit the invention are, for instance, halogenated hydrocarbons like the freons and stable fluorinated chalcogenides like  $SF_6$ ,  $SeF_6$  and the like (page 6, lines 38-39). Further, the reference teaches a preparation of such kind will keep indefinitely in this state and can be used at any time for diagnosis, provided it is dispersed into sterile water before injection (page 4, lines 40-42). Thus, the reference teaches that the powder is stored solely in a container and the liquid carrier is stored in a different container which reads on instant claims 24 and 32.

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The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

2. Claims 16-32 and 47-52 are rejected under 35 U.S.C. 103(a) as being unpatentable over Schneider et al. EP 0554213 (Schneider) in view of Hugh D. Van Liew, Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, *J Appl Physiol* 82:2045-2053, 1997 (hereinafter Hugh).

Schneider is relied upon for the reasons set forth hereinabove.

Schneider did not disclose literally the different pressure values required by claims 18-20 and 25-27.

However the reference teaches that it has been surprisingly found that for gases where the pressure difference  $DP = P_{25} - P_{75}$  exceeds a value of about 25 - 30 Torr, the killing effect of the blood pressure on the gas-filled microvesicles is minimized, i.e. the actual decrease in the bubble count is sufficiently slow not to impair the significance, accuracy and reproducibility of echographic measurements.

In addition, Hugh teaches Stabilized bubbles in the body: pressure-radius relationships and the limits to stabilization, the reference discloses that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to ensure that the pressure inside the gas microvesicles disclosed by Schneider and apply the knowledge that negative pressure inside the bubble to counter the tendency for outward diffusion of the gases as disclosed by Hugh. The person of ordinary skill would be able to determine the right amount of pressure used inside the bubble according to the equation disclosed by Schneider that where the pressure difference  $DP = P_{25} - P_{75}$  exceeds a value of

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about 25 - 30 Torr. The skilled artisan would have expectations of success to have a composition for contrast agent in an aqueous suspension containing gas-filled microvesicles useful in imaging.

### ***Double Patenting***

3. Claims 16, 21-24, 28-32 and 47-52 remain rejected on the ground of nonstatutory obviousness-type double patenting as set forth in the office action dated 10/24/2008.
4. Claims 16, 21-24, 28-32 and 47-52 remain provisionally rejected on the ground of nonstatutory obviousness-type double patenting as set forth in the office action dated 10/24/2008.

### ***Response to Arguments***

Applicant's arguments with respect to claims 16, 17, 21-24, 28-32 and 47-52 have been considered but are moot in view of the new ground(s) of rejection.

### ***Double Patenting***

- Like Toumier, the cited patents and applications fail to teach or suggest the claimed compositions or containers comprising a dried material and a gas at reduced pressure as required by the instant claims. In each of the cited patents and applications, any precursor compositions used to prepare contrast agents comprise a gas at atmospheric pressure, not the gas at reduced pressure instant claims. Moreover, as explained above, Vasa Liew, which neither teaches nor suggests contrast agent precursors, fails to remedy this deficiency.

To respond: as discussed *supra*, even if it did not teach literally that the pressure of the gas should be less than atmospheric pressure, Hugh is relied upon for teaching that the crucial aspect of a structural stabilizer is that it must produce a negative pressure inside the bubble to counter the tendency for outward diffusion of the gases inside (page 2045, right column).. Thus the rejection is maintained.

***Correspondence***

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Nabila G. Ebrahim whose telephone number is 571-272-8151. The examiner can normally be reached on 8:00AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Hartley can be reached on 571-272-0616. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Nabila G Ebrahim/  
Examiner, Art Unit 1618

/Michael G. Hartley/  
Supervisory Patent Examiner, Art Unit  
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